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Skin Conductance at Baseline and Post-Heel Lance Reflects Sympathetic Activation in Neonatal Opiate Withdrawal

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Abstract

Aim—Skin conductance (SC) provides an objective measure of autonomic system regulation through sympathetic-mediated filling of sweat glands. This study aimed to test the utility of SC to detect sympathetic activation in neonatal abstinence syndrome (NAS).

Methods—14 term (mean, SE: 38.8 ± 0.35 weeks gestational age) neonates with chronic prenatal opiate exposure were enrolled. SC (peaks/sec and mean of peaks) were measured at baseline, during heel lance/squeeze (HLS) and recovery from HLS at 24-48 (mean 38) hours of life prior to treatment for NAS. Blinded coders with established reliability assessed neonates using the Modified Finnegan Neonatal Scoring System (MFNSS). Non-parametric tests were used to determine group differences, phase differences from baseline to HLS and HLS to recovery, and associations between MFNSS and SC measures.

Results—Neonates that would later require morphine treatment for NAS (n = 6) had higher baseline SC mean of peaks than those that did not require treatment (n = 8) ($P<0.05$). Moreover, there were unique phase differences between groups and SC positively correlated with MFNSS ($P< 0.05$).

Conclusion—SC provides early identification of NAS severity. However, a larger sample is needed to determine sensitivity and specificity of SC for early identification of NAS and treatment effectiveness.

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CONFLICT OF INTEREST

None

INTRODUCTION

Opioid use in pregnancy is an important public health issue. Both prescribed and illicit opiate use in pregnancy is on the increase (1). The 2010 National Survey on Drug Use and Health reported that an estimated 4.4% of pregnant women admitted to illicit drug use in the past 30 days(2). Neonates born to chronic opioid users are at risk for developing Neonatal Abstinence Syndrome (NAS), a constellation of acute manifestations of opioid withdrawal which presents early in the postnatal period. The epidemic is sizeable such that by 2009, one infant per hour was born with NAS in the United States (3, 4). The use of prescription opiate use amongst pregnant women is a growing concern, with increased incidence of NAS symptoms and low birth weight in exposed infants (5). Opioids act by inhibiting the release of norepinephrine at synaptic terminals. A sudden discontinuation of exogenous opiates results in higher levels of norepinephrine, characterized by central nervous system irritability and gastrointestinal dysfunction (6). NAS clinical manifestations commonly include irritability, tremors, seizures, sweating, high-pitched cry, temperature instability, tachypnea, uncoordinated suck/swallow reflexes, feeding difficulties, vomiting and diarrhea (6). The onset and severity of these symptoms can vary depending on the type of opioid the infant was exposed to in utero. According to the Center for Substance Abuse and Treatment, infants exposed to methadone may exhibit withdrawal symptoms anytime in the first 2 weeks of life, but usually do so within 72 hours of birth, with symptoms lasting days to weeks, whereas infants exposed to buprenorphine develop symptoms within 12–48 hours of birth that peak at 72–96 hours and resolve by 7 days (7). The consequences of acute opioid withdrawal in neonates may be severe, resulting in significant morbidity and even mortality for some. Furthermore, those infants afflicted with NAS remain at risk for long-term adverse neurobehavioral outcomes (8, 9).

Early diagnosis and treatment of NAS is critical for promoting the best outcomes for these infants. The Finnegan Scoring System remains the most commonly used tool for the diagnosis of NAS, though it is known to be quite subjective (10, 11). Therefore the need for an objective measure in the assessment NAS is underscored.

Skin conductance (SC) provides real time, continuous measurement of sympathetic nervous system (SNS) activity that has potential for use in NAS diagnosis and monitoring. SC reflects bursts of SNS activity through detection of palmar and plantar sweating. Sweat release is controlled by the cholinergic sympathetic nervous system, as well as increased catecholamine response following a stressful condition (12).This is particularly increased in the palms and soles, where the stratum corneum, epidermis, and eccrine sweat glands are dense. With sympathetic activation, there are quantifiable increases in the number and amplitude of electrodermal or skin conductance responses. The use of SC has been well documented in term and preterm infants with conditions associated with pain, stress, and arousal (12-15). SC also has been demonstrated to be a better measure of SNS activation than heart rate or blood pressure, because it is not affected by hemodynamic variability (16). However, what is unknown is the extent to which SC provides information on SNS activation associated with neonatal opiate withdrawal. The primary aim of this study was to test the utility of skin conductance (SC) to detect sympathetic activation in neonatal abstinence syndrome (NAS). We hypothesized that those infants with high skin conductance

levels at baseline and with a painful stimulus such as a heel lance would also have high scores on the Modified Finnegan Neonatal Scoring System (MFNSS) and require pharmacological intervention.

METHODS

Ethics

The study protocol was reviewed for ethical and regulatory compliance and approved by the institutional review board at the study site. Informed, written parental consent was obtained for each study subject.

Participants and setting

This study was an observational, feasibility study with each NAS infant serving as her/his own control. The setting was a level IV tertiary referral neonatal intensive care unit (NICU) and a newborn nursery, located within an academic medical center in south central Pennsylvania, USA. Fourteen term NAS infants, post-menstrual age of 37weeks to 41 weeks, with hemodynamic and cardio-pulmonary stability after birth, were enrolled during November 2012 to January 2014. Mothers of study subjects were identified by the perinatologist providing care to be opiate dependent, with chronic use during pregnancy (defined as greater than one intrapartum month), but without other significant co-morbidities (i.e. diabetes, pre-eclampsia). Exclusion criteria were: infants requiring mechanical ventilation, major congenital anomalies, hypoglycemia, perinatal exposure to magnesium sulphate, and maternal poly drug use.

Procedure

A review of the electronic medical record (EMR) was performed for detailed maternal medical history and neonatal demographics including: Apgar scores, exposure to magnesium sulphate, anesthetic agents, and NAS symptomatology and treatment course. Following birth, all study infants were admitted to the newborn nursery to room-in with their mothers, per standard clinical practice. Prenatal exposure to opiates was confirmed by positive toxicology of infants' meconium.

The standard duration for observation and monitoring of NAS, using the Modified Finnegan Neonatal Scoring System (MFNSS) was five days. Infants with scores consistently low on MFNSS (below 8) were discharged after five days of observation, while the infants with three consecutive scores above 8, or two scores averaging more than 8, were admitted to the NICU for further assessment and treatment.

The evaluation of infant response to noxious stimuli was done by observing the response to blood sampling (heel lance/squeeze) performed as part of the state mandatory newborn metabolic screen done at 24-48 hours of age. This was an observation of routine care, thus infants were not subjected to any painful stimulus as part of the research. Study infants were given standard routine comfort care prior to and during the blood sampling , which included use of non-nutritive sucking, facilitating self-consoling supportive measures (hands to face, bracing of extremities), and providing tucked and flexed positioning with a snug wrap. Heel

lance was performed using a standard lancet, by an experienced nurse after 10 minutes of baseline skin conductance (SC) recording. SC measurement continued during the heel lance and squeezing for blood collection, and for additional 10 minutes following completion of blood collection. The heel lance was performed preferentially on the opposite foot, to avoid artifact movement to the SC electrodes. During the baseline phase there was no direct stimulation (i.e. handling or care). The stimulus phase, on the other hand, consisted of heel warming, skin prep, and the *pain phase* beginning with heel-lance through termination of heel squeeze during which the infants' responses were measured. The *recovery phase* was the 10-minute period following heel-lance/squeeze. SC measures were obtained continuously during the 30 minute observation period, and later analyzed off-line in baseline, stimulus, and recovery epochs. Figure 1 depicts a sample registration of SC.

Skin conductance apparatus and software

Skin conductance (SC) activity was measured using the Med-Storm TM device (MedStorm, Oslo, Norway). The electrical conductance measured by low frequency indicates the ionic conduction across the stratum corneum of the skin, determined by sweat duct filling (17). To measure SC activity, three surface electrodes (Conmed ® Corporation, Utica NY, USA) were applied to the infants' foot as directed by the manufacturer (18). The electrode system consists of a measuring electrode, a counter current electrode, and a reference voltage electrode, to ensure a continuous applied voltage across the stratum corneum beneath the measuring electrode, as previously described (18-21).

The observation/measurement session was standardized to time of day (afternoons, between 12-4pm) and was done after nursing care and post-feeding, in a quiet area with low light and ambient temperature, to control for extraneous factors known to impact autonomic system measurement (i.e. circadian fluctuations, feeding and handling cycles) (13, 22). In addition, we ensured that no painful procedure, such as circumcision or phlebotomy, occurred on the day that we obtained SC measures. Skin conductance data were analyzed offline, using a software package provided by the manufacturer (Med Storm Innovation, Oslo Norway). SC measures included the number of electrodermal responses (EDRs) over time, expressed as *peaks/sec*, the average amplitude of the response, expressed as *mean of peaks* (μsiemens), and the background, or unstimulated *basal level* (μsiemens). While the basal activity could be dominated not by sympathetic activation per se but by a general restlessness, peaks per second and mean amplitude of peaks represent the strength and sustainability of each sweat gland burst and thus are most representative of sympathetic arousal. In addition, Storm has shown that by processing this signal with filtering both 'noise' and potential artifacts can be minimized (14).

Inter-observer reliability for Modified Neonatal Finnegan Scoring System

Nursing education related to the assessment and scoring of newborns experiencing NAS is included in the orientation for new nurses. Depending on prior experience, nurses hired for the well-baby nursery (WBN) and the neonatal intensive care unit (NICU) receive additional didactic training as self-study or classroom format. The training content is based upon the Gateway Health Plan DVD, Neonatal Abstinence Syndrome: Assessing the Infant, available

from: https://www.gatewayhealthplan.com/sites/default/files/documents/PAMA_neonatal.pdf

For this study, eight nurses with expertise in the care of NAS infants were identified. These nurses completed an additional independent study of Assessing Signs & Symptoms of Neonatal Abstinence Using the Finnegan Scoring Tool: An Inter-Observer Reliability Program© http://www.neoadvances.com/ . The program included a review of scoring criteria and an assessment of an infant case scenario, followed by a comparison of the participant's MFNSS score with that of the expert author. Successful completion of the program required a minimum 90% agreement with the author. Approximately 6 months after the initial inter-observer reliability assessment, a second assessment was completed to ensure ongoing inter-rater agreement >85% as has been previously described (23).

Statistical analysis

SPSS (IBM version 21, Chicago, Illinois) was used for data entry and analyses. Mann-Whitney U (non-parametric test) was used to compare continuous variables between treated and non-treated groups, while Spearman's correlation coefficients were used to test the relationships between the Finnegan scores and the SC measures. For within group comparisons, Wilcoxon Signed Rank tests were used to test phase differences in SC response at baseline (pre heel lance/squeeze) with pain phase (heel lance/squeeze), and pain phase with recovery phase (post-heel lance/squeeze). A value of $P<0.05$ was used for all tests of significance.

RESULTS

Demographic information

Fourteen term infants that met the eligibility criteria for the study were enrolled. The mean ± SE gestation for infants was 38.8 ±0.35weeks; birth weight was 2850.8±120 grams; and 11(78.6%) were delivered vaginally. None of the study infants was depressed at birth; their median 5-minute Apgar score was 9 (7-9). None of those enrolled required pharmacologic treatment for NAS (MFNSS scores were below 8) at the time of the baseline SC measurements. Six (43%) of the infants studied required subsequent treatment for NAS with morphine by 72 hours of life. Seventy percent of subjects' mothers were identified by the maternal and fetal medicine (MFM) team and maintained on the methadone program. Other opiate use (i.e. morphine, buprenorphine and oxycodone) in mothers accounted for 30% of substance use. All study mothers reported to continue cigarette smoking during this pregnancy. Infant and maternal characteristics are presented in Table 1.

Descriptive results

The measurement session lasted mean ±SE duration of 30.1 ± 1.1 minutes and occurred between 24-48 hours of life (mean 38hrs of life). MFNSS done by nurse coders within 1-2 hours of the SC measurement was median (IQR) of 5 (4-10) for the full sample and 10 (8-12) and 4 (3-5) for treatment and non-treatment groups respectively. Skin conductance obtained at baseline (pre-heel lance/squeeze) for the full sample was basal of 12.7 ±11.5 μsiemens, peaks/sec of 0.22 ± 0.3, and mean of peaks of 0.07 ±0.1 μsiemens. There was a

marked difference between groups at baseline such that those infants with 3-fold higher values of skin conductance measures across all three parameters (basal, peaks/sec, and mean of peaks) later required pharmacologic treatment for NAS.

Between and within group differences

Both gestational age (GA) and postnatal age in hours at the time of measurement were similar between groups. Infants in the group requiring later treatment with morphine by 72 hours of life had higher birthweights; however, none of the study infants were large for gestational age at birth (Table 2). The results of a *two-group comparison* indicated that infants with higher basal skin conductance levels at baseline (pre-heel lance/squeeze) and higher SC mean of peaks at both baseline and recovery (post-heel lance/squeeze), later required treatment with morphine by 72 hours of life (Table 2). There were no SC differences between groups during the pain phase (heel lance/squeeze). However, for the within group comparisons there were significantly higher *phase differences* in peaks/sec from baseline to pain phase, and pain phase to recovery in the non-treatment group; with P values of 0.01 and 0.03 by Wilcoxon Signed Rank tests, respectively. Conversely, those infants that would later require treatment for NAS by 72 hours of life had a significant *phase difference* in peaks/sec from pain phase to recovery of P = 0.04.

Correlations

In the full sample of infants (N=14), the baseline (pre-heel lance/squeeze) SC mean of peaks showed a direct positive correlation with MFNSS, with Spearman's correlation coefficient of 0.65, P=0.01(Figure 2). Basal SC also was directly correlated with MFNSS, with Spearman's correlation coefficient of 0.58, P=0.03. In contrast, peaks/sec did not correlate with MFNSS.

DISCUSSION

To our knowledge, there are no published studies in NAS infants that have examined infants' sympathetic arousal to noxious stimuli using skin conductance. The results of the present study revealed that infants that had higher SC mean of peaks during both baseline (pre-pain) and recovery (post-pain) phases at less than 48hrs went on to require pharmacologic treatment with morphine by 72 hours of age. The height of mean peak amplitude of SC, strength of the sweat gland burst, represents higher sympathetic activation in these infants.

A second key finding in this investigation, is that there were clear differences in pain responses (during heel lance/squeeze) when comparing the group of infants that would not require pharmacologic treatment for opiate withdrawal as opposed to those infants that needed morphine treatment for NAS by 72 hours. Those infants that would not require later pharmacotherapy for NAS had significant increases in SC responses (peaks/sec and mean of peaks) during both the pre-pain to pain phase, and the pain to recovery phase, showing an expected sympathetic response to the pain stimulus of heel lance/squeeze for blood sampling. In contrast, those infants that would later require pharmacotherapy for NAS by 72 hours had markedly higher baseline (pre-pain) peaks/sec than those that did not require

subsequent treatment, and in this group there was only a single between phase differences in peaks/sec from the pain to recovery phase. We speculate that fewer phase differences in the treatment group were secondary to an already high sympathetic arousal phenomenon at baseline (pre-pain stimulus), or a “ceiling effect”, such that, even with a painful stimulus no further arousal occurred.

Our findings are consistent with other studies which have shown mean of peaks and peaks/sec increase significantly with stimuli such as heel lance, noise, and other stimuli (12, 13, 18, 24). Dalal et al (2013) reported a similar finding when SC was applied in post-operative pediatric (6-12 months of age) patients recovering from anesthesia. In this study, the mean of peaks and basal levels were more sensitive measures of autonomic arousal than peaks/sec in the post-operative period in pediatric patients (25)**.** They analyzed acute behavioral pain scores and SC measures, finding that peak amplitude of SC served as the best indicator of significant pain in a sample of older infants. In 2000, Storm found SC amplitude (peaks) and number of waves (peaks/s) increased in response to heel lance, and returned to pre-heel lance levels in preterm infants >29 weeks gestational age (14). In a recent study of preterm infants 22-27 weeks GA, investigators found the combination of both heel lance and heel squeeze produced significant rises in SC peaks/s (26). Gladman et al. examined healthy term and post-term infants’ baseline and SC responses to heel lance of varied postmenstrual ages. In the two subgroups of infants 36-39 weeks and 40-43 weeks GA, investigators found a sharp rise from baseline SC to heel lance for each of the groups at 30% and 95% respectively. While the gestational age of infants in this study was similar to the infants in our study, these were healthy infants without known exposure to opiates (19) .

In our study, we noted variations in the SC measures between patients. This suggests a within-person variability of response to stimuli; this in part may relate to individual variation in response to environmental challenge (12, 27). It is notable; however, that the infants that would require pharmacologic treatment for withdrawal within 24 hours of our observation, had significantly higher baseline (pre-pain phase) mean of peak SC values, and persistently elevated mean of peak SC levels in recovery (post-pain phase). In contrast, those infants that did not require later pharmacologic treatment had peak SC values which increased during pain phase and returned to baseline during the recovery phase. The findings of this study also indicate direct positive correlation between the mean of peaks SC during the pre-pain phase with pre-stimulation Finnegan scores.

The strengths of this study are its prospective nature and application to a population with well described pathophysiology and relative control of environmental and circadian influences known to impact SC measurement, such as time of day, infant’s behavioral state, handling, noise, temperature, ambient light and other noxious influences. We studied only opiate exposed infants with similar maternal/infant characteristics and excluded poly-drug exposed infants. Our approach to design and analysis included not only group differences, but also within group patterns of response where we identified unique phase differences among groups. This study used a standardized approach to obtaining both biological and behavioral measures of response for each study subject. Moreover, the abstinence scoring with MFNSS was done with pre-established inter-rater reliable nurse coders who were blinded to study aims and SC results.

The major limitation of this study was our small sample size. However, we found statistically significant between group and within group differences in skin conductance. Observing serial measures of SC responses to daily care (i.e. sound and tactile stimuli) may have proven useful in characterizing non-painful sympathetic arousal (i.e. responses to care, handling) in this sample of infants. Including a comparison group of healthy term infants not exposed to opiates also may have proven useful. These approaches were considered but not undertaken in this small scale feasibility study. Time constraints related to additional assurances that would be required by the IRB to obtain parental authorization for screening infants for opiates, not part of standard care, the costs that would be incurred for the screening, and the sensitive nature of disclosure of the information influenced our decision to not study a "control" group of infants in this pilot study.

CONCLUSION

Skin conductance measures were noted to be higher at 24-48 hours of life (mean age of 38hours) at baseline (pre-pain) and recovery (post-pain) in neonates that subsequently required morphine treatment by 72 hours of life for NAS, in support of our hypothesis. The SC measures were highly correlated with the MFNSS scores at 24-48hours of life. This finding has relevance as neonates with higher MFNSS scores typically require pharmacological therapy. Suggesting, skin conductance may be useful as an important *early* objective adjunct to MFNSS for predicting which infants will require later pharmacologic treatment. Skin conductance may be of particular importance not only in the early identification of NAS severity, but also in later therapeutic monitoring of NAS treatment. Further applications of these findings hold promise for the development of an early risk assessment to identify which neonates may require an extended period of observation and treatment for the symptoms of withdrawal.

In summary, we suggest that SC can be used effectively with MFNSS as an adjunct in the assessment of symptoms in NAS. The non-invasive nature of SC measurement, as well as its portability makes it an attractive tool that may permit *continuous* real-time monitoring of sympathetic arousal as seen with NAS. However, further study is required in a larger sample to determine the sensitivity and specificity of SC for detection of sympathetic arousal by NAS severity before it can be recommended for clinical application to this population and setting.

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List of Abbreviations

NAS	Neonatal Abstinence Syndrome
MFNSS	Modified Finnegan Neonatal Scoring System
SC	Skin Conductance
GA	Gestational Age
BW	Birth Weight
HLS	Heel Lance/Squeeze
WBN	Well Baby Nursery
NICU	Neonatal Intensive Care Unit
MFM	Maternal Fetal Medicine
SE	Standard Error
EMR	Electronic Medical Record
IQR	Inter Quartile Range
EDR	Electrodermal Response (Peaks/s)

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Key Notes

- Sympathetic-mediated sweat gland filling from emotional distress or pain of heel-lance/squeeze was measured non-invasively via surface electrodes and recorded electronically.
- Skin conductance at baseline and recovery detected higher levels of sympathetic activation prior to the need for pharmacotherapy for neonatal abstinence syndrome (NAS).
- These preliminary findings will inform future investigations to evaluate the sensitivity and specificity of skin conductance as a test of NAS severity and treatment effectiveness.

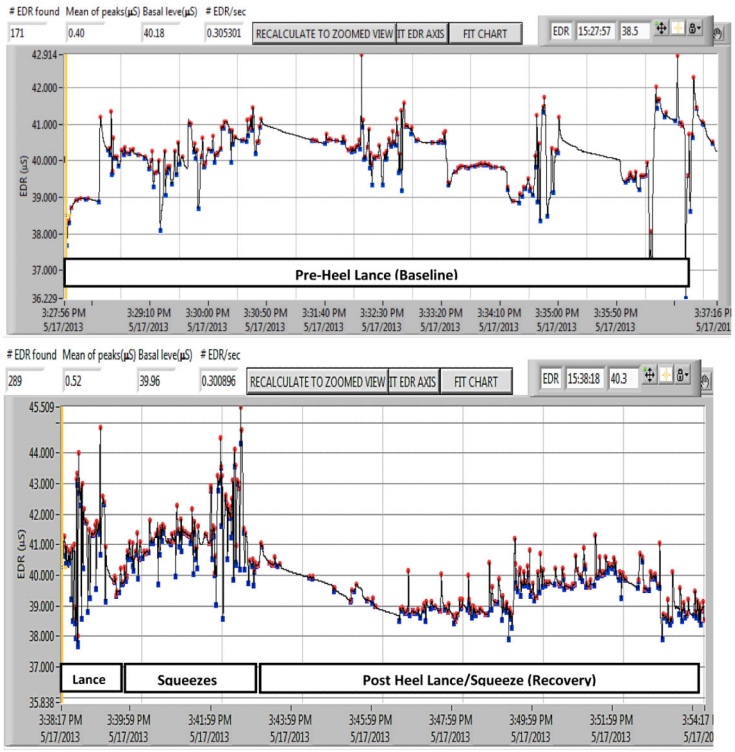

Figure 1.

Representative subject from NAS treatment group showing continuous SC data measured around blood sampling done prior to the need for pharmacologic intervention for NAS. Ten minutes of baseline data were obtained prior to the blood sampling, next, during blood sampling showing noxious effects of both lance and heel squeezing, and during the 10 minutes of recovery (post-sampling). Each waveform *peak* (or electrodermal response-EDR) is noted by a red dot. The *frequency of peaks* divided by the total time of the epoch in seconds is EDR/sec or *peaks/sec*. The mean height of the peaks is noted as *mean of peaks*.

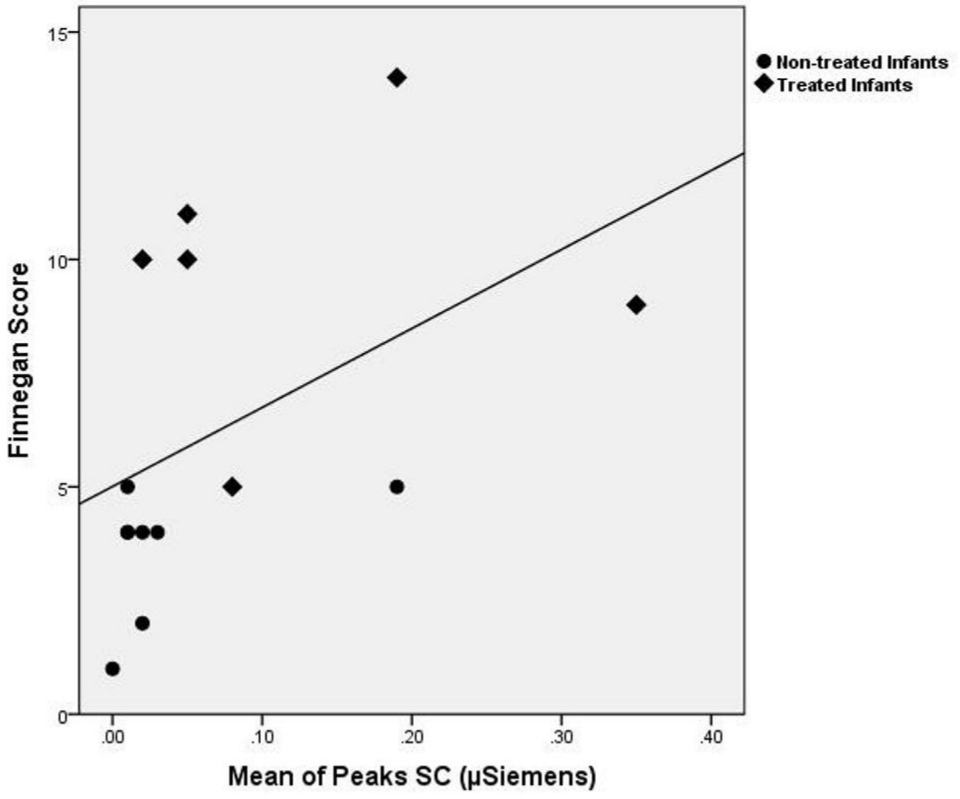

Figure 2.

Correlation between skin conductance mean of peaks (μS) from the pre-heel lance phase and the modified Finnegan Neonatal Scoring System for infants prior to the initiation of pharmacologic intervention (treatment group vs non-treatment group, represents those requiring later treatment at 72hrs vs those not requiring treatment). The Spearman's (r_s) correlation coefficient is 0.65 (P= 0.01).

Table 1

Infant and maternal characteristics of the 14 subjects

Infant Characteristics	**mean ± SE, n, % median (IQR)**
Gestational age at birth, *wks*	38.8 ± 0.35
Birth weight, *g*	2850 ± 120
Gender	
Female	5, 36
Male	9, 64
5-min Apgar Score	9 (7-9)
Mode of Delivery	
Vaginal Delivery	11, 79
C-section	3, 21
Treated for NAS	
Yes	6, 43
No	8, 57
Maternal Characteristics	**mean ± SE, n, %**
Age, *yrs*	25 ± 1.14
Level of Education	
High School	8, 57
College	6, 43
Prenatal Care	
Yes	14, 100
Substance Use in Pregnancy	
Methadone	10,70
Other Opiates	4, 30
Cigarette Smoking during index pregnancy	14,100

Table 2

Between group comparisons of infants' characteristics and skin conductance measures

	Non-treated infants mean± (SE) n=8	**Treated infants mean± (SE) n=6**	***P*value**
Infants' Characteristics *			
GA-weeks	38.3 (0.41)	39.5 (0.51)	0.949
Age in hours at time of SC	38 (3.16)	35 (3.40)	0.347
BW-grams	2665 (98.8)	3098 (219.5)	0.025
SC Measures †			
Baseline (Pre-HLS)			
Mean of Peaks, μsiemens	0.04 (0.06)	0.12 (0.13)	0.020
Peaks/Sec, μsiemens	0.10 (0.08)	0.38 (0.44)	0.059
Basal Level, μsiemens	6.17 (2.71)	21.47 (13.22)	0.029
Pain Phase (HLS)			
Mean of Peaks, μsiemens	0.10 (0.11)	0.32 (0.34)	0.435
Peaks/Sec, μsiemens	0.27 (0.17)	0.40 (0.19)	0.222
Basal Level, μsiemens	6.02 (2.75)	19.92 (14.09)	0.065
Recovery Phase (Post-HLS)			
Mean of Peaks, μsiemens	0.04 (0.06)	0.26 (0.17)	0.048
Peaks/Sec, μsiemens	0.09 (0.10)	0.21 (0.20)	0.268
Basal Level, μsiemens	6.15 (2.89)	16.43 (13.66)	0.073

HLS = Heel lance/squeeze,

*Difference by Independent samples t test,

†Difference by Mann Whitney U test